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EP 0365763 A EP 0316857 A

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UK CL (Edition L) C2C CLW CLZ CRM CSJ
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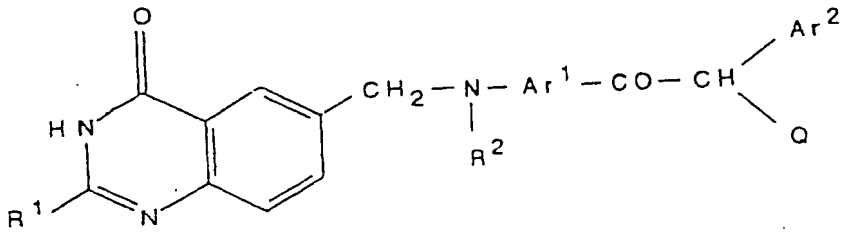
(54) Quinazoline derivatives

(57) Quinazoline derivatives of the formula I



wherein
R^1 is hydrogen or a defined substituent, e.g. amino, (1 - 4C) alkyl and (1 - 4C) alkoxy;
R^2 is hydrogen, (1 - 4C) alkyl, which can be substituted by certain substituents (3 - 4C) alkenyl or (3 - 4C) alkynyl;
Ar^1 is phenylene or a 5- or 6-membered aromatic heterocyclene ring;
Ar^2 is optionally substituted phenyl or heteroaryl; and
Q is a defined substituent e.g. nitro, cyano, carbamoyl, (1 - 4C) alkylsulphonyl and N,N-di-[(1 - 4C) alkyl]sulphamoyl;
or pharmaceutically-acceptable salts thereof; are useful as anti-tumour agents.

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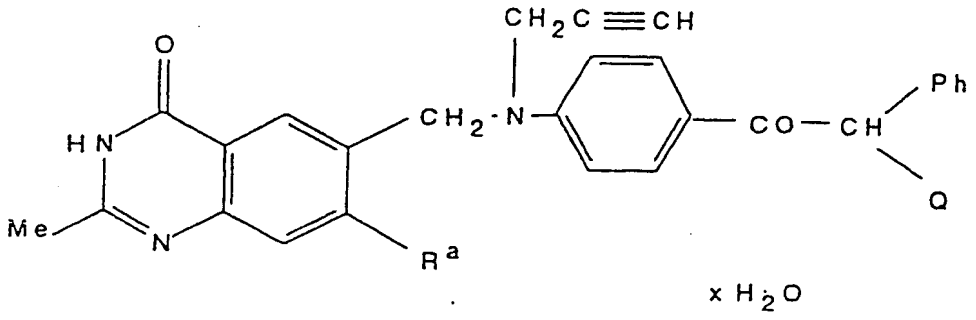
3-(pivaloyloxymethyl)-3,4-dihydroquinazolin-6-ylmethyl]-N-(prop-2-ynyl)amino}benzoate and the appropriate nucleophile was used in place of benzyl methyl sulphone there were obtained the quinazoline derivatives described in the following Table, the structures of which were confirmed by proton magnetic resonance and mass spectroscopy and by elemental analysis.

TABLE I



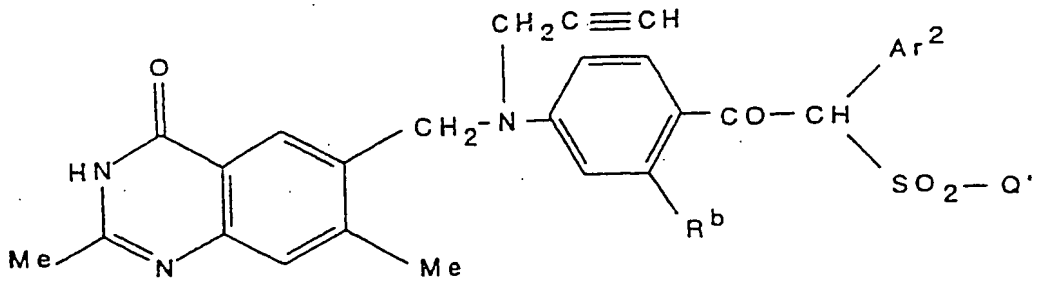
Example 6 Compound No.	R^a	Q	x	m.p. (°C)
1[a]	H	cyano	-	113-115
2	Me	methylsulphonyl	0.5	236-242
3[b]	Me	isopropylsulphinyl	0.5	190-194
4[c]	Me	isopropylsulphonyl	0.2	262-265
5[d]	Me	benzylsulphonyl	0.7	279-281
6[e]	H	N,N-dimethylsulphamoyl	0.4	122-124
7[e,f]	Me	N,N-dimethylsulphamoyl	-	143-151
8[g]	Me	N-methylsulphamoyl	-	134-153
9[h]	Me	morpholinosulphonyl	0.5	166-170

Notes

a. The product was purified by reverse-phase chromatography using decreasingly polar mixtures of water, methanol and trifluoroacetic acid as eluent. The product so obtained contained

mass spectroscopy and by elemental analysis.

TABLE II



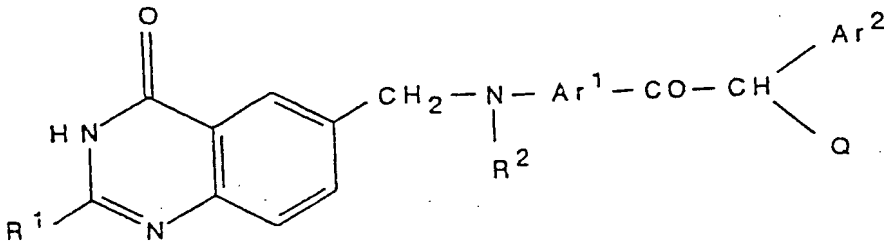
Example 17 Compound No.	R^b	Ar^2	Q'	m.p. (°C)
1[a]	H	3-pyridyl	methyl	190-192
2[b]	F	p-fluorophenyl	methyl	171-173
3[c]	F	p-cyanophenyl	methyl	173-174
4[d]	F	p-fluorophenyl	4-pyridyl	198-199
5	H	p-fluorophenyl	methyl	163-166
6[e]	F	p-tolyl	methyl	-
7[f]	H	p-fluorophenyl	dimethylamino	163-165
8	H	p-fluorophenyl	morpholino	155-158
9[g]	F	p-fluorophenyl	N-(2-dimethyl-aminoethyl)-N-methylamino	134-135
10[h]	F	p-fluorophenyl	4-tert-butoxy-carbonyl-piperidin-1-yl	142-144
11[i]	F	2-pyridyl	methyl	-
12[j]	F	3-pyridyl	methyl	173-175

Notes

a. The product contained 1 equivalent of water.
The methyl 3-pyridylmethyl sulphone used as a starting

CLAIMS

1. A quinazoline derivative of the formula I



I

wherein R^1 is hydrogen, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, piperidino, morpholino, piperazin-1-yl, 4-[(1-4C)alkyl]piperazin-1-yl, 4-[(2-4C)alkanoyl]piperazin-1-yl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl, 4-[(1-4C)alkyl]piperazin-1-yl-(1-4C)alkyl, 4-[(2-4C)alkanoyl]piperazin-1-yl-(1-4C)alkyl, N-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[hydroxy-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[hydroxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkoxy-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, N-[di-(1-4C)alkylamino-(2-4C)alkyl]-N-(1-4C)alkylamino-(1-4C)alkyl, N,N-di-[di-(1-4C)alkylamino-(2-4C)alkyl]amino-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, carboxy-(2-4C)alkanoyloxy-(1-4C)alkyl, [illegible]carbonyl-(2-4C)alkanoyloxy-(1-4C)alkyl, hydroxy-

the quinazoline ring may optionally bear at the 5-, 7- or 8-position one further substituent selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

R^2 is hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-4C)alkynyl, hydroxy-(2-4C)alkyl, halogeno-(2-4C)alkyl or cyano-(1-4C)alkyl;

Ar^1 is phenylene or a 5- or 6-membered aromatic heterocyclene ring which contains up to 3 heteroatoms selected from nitrogen and sulphur, each of which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy;

Ar^2 is phenyl or heteroaryl which may optionally bear one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy; and

Q is nitro, cyano, carbamoyl, sulphamoyl, (1-4C)alkoxycarbonyl, di-[(1-4C)alkoxy]phosphoryl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenyl-(1-4C)alkylthio, phenyl-(1-4C)alkylsulphinyl, phenyl-(1-4C)-alkylsulphonyl, heteroarylthio, heteroarylsulphinyl, heteroarylsulphonyl, heteroaryl-(1-4C)alkylthio, heteroaryl-(1-4C)alkylsulphinyl, heteroaryl-(1-4C)alkylsulphonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-[(1-4C)alkyl]sulphamoyl, morpholino-sulphonyl, piperidinosulphonyl, piperazin-1-ylsulphonyl or 4-(1-4C)-alkylpiperazin-1-ylsulphonyl, and when Q is a group comprising a phenyl or heteroaryl group, said phenyl or heteroaryl group may optionally bear one substituent selected from halogeno, cyano, hydroxy, amino, (1-4C)alkyl and (1-4C)alkoxy;

and wherein the heteroaryl group when Ar^2 is heteroaryl, or the heteroaryl group when Q is a heteroaryl-containing group, is a 5- or 6-membered heteroaryl ring which contains 1 or 2 nitrogen heteroatoms and optionally contains a further heteroatom selected from nitrogen, oxygen and sulphur;

or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative of the formula I as defined in claim 1 wherein, in addition, Q is 4-(1-4C)alkoxycarbonylpiperazin-1-

ylsulphonyl, N-[amino-(2-4C)alkyl]sulphamoyl, N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl, N-[di-[(1-4C)alkyl]amino-(2-4C)alkyl]sulphamoyl, N-(1-4C)alkyl-N-[amino-(2-4C)alkyl]sulphamoyl, N-(1-4C)alkyl-N-[(1-4C)alkylamino-(2-4C)alkyl]sulphamoyl or N-(1-4C)alkyl-N-[di-[(1-4C)alkyl]amino-(2-4C)alkyl]sulphamoyl; or a pharmaceutically-acceptable salt thereof.

3. A quinazoline derivative of the formula I as claimed in claim 1 wherein R^1 is methyl, hydroxymethyl, methoxymethyl, methylaminomethyl, dimethylaminomethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl or 4-methylpiperazin-1-ylmethyl; the quinazoline ring may optionally bear a 7-fluoro, 7-chloro or 7-methyl substituent;
R^2 is methyl, ethyl, propyl, prop-2-enyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene which may optionally bear one fluoro substituent, or Ar^1 is thiophene-2,5-diyl or thiazole-2,5-diyl with the group $-CO-CH(Ar^2)(Q)$ in the 2-position;
Ar^2 is phenyl which may optionally bear a substituent selected from fluoro, chloro, nitro, trifluoromethyl or methyl; and
Q is nitro, cyano, carbamoyl, sulphamoyl, methoxycarbonyl, ethoxycarbonyl, dimethoxyphosphoryl, diethoxyphosphoryl, methylsulphinyl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphinyl, phenylsulphonyl, benzylsulphinyl, benzylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

4. A quinazoline derivative of the formula I as claimed in claim 1 or claim 2
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group $-CO-CH(Ar^2)(Q)$ in the 1-position) or pyridine-2,5-diyl (with the group $-CO-CH(Ar^2)(Q)$ in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl, 3-nitrophenyl,

4-cyanophenyl, 2-pyridyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl, morpholinosulphonyl, piperazin-1-ylsulphonyl or N-methyl-N-(2-dimethylaminoethyl)sulphamoyl;
or a pharmaceutically-acceptable salt thereof.

5. A quinazoline derivative of the formula I as claimed in claim 1 or claim 2
wherein R^1 is methyl;
the quinazoline ring may optionally bear a 7-methyl substituent;
R^2 is methyl or prop-2-ynyl;
Ar^1 is 1,4-phenylene, 2-fluoro-1,4-phenylene (with the group $-CO-CH(Ar^2)(Q)$ in the 1-position) or pyridine-2,5-diyl (with the group $-CO-CH(Ar^2)(Q)$ in the 2-position);
Ar^2 is phenyl, 3-fluorophenyl, 4-fluorophenyl or 3-pyridyl; and
Q is diethoxyphosphoryl, isopropylsulphinyl, methylsulphonyl, isopropylsulphonyl, phenylsulphonyl, benzylsulphonyl, 4-pyridylsulphonyl, N-methylsulphamoyl, N,N-dimethylsulphamoyl or morpholinosulphonyl;
or a pharmaceutically-acceptable salt thereof.

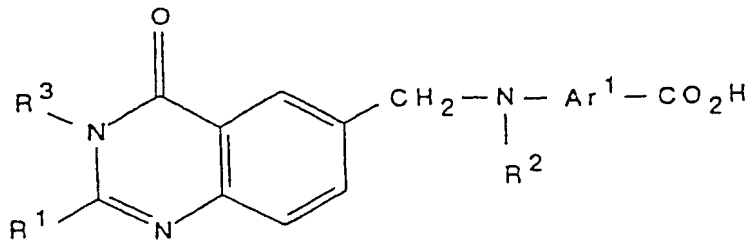
6. A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in claim 1, selected from:-
4-[N-(2-methyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin,
4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin and
N,N-dimethyl-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide.

7. A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in claim 1 or claim 2, selected from:-

4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-isopropylsulphonyldesoxybenzoin,
N,N-dimethyl-p-fluoro-α-{p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide, 2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin, N,N-dimethyl-p-fluoro-α-{o-fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzoyl}-α-toluenesulphonamide,
4'-fluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-methylsulphonyldesoxybenzoin,
2,4'-difluoro-4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-α-morpholinosulphonyldesoxybenzoin,
α-{5-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]pyridine-2-carbonyl}-p-fluoro-N,N-dimethyl-α-toluenesulphonamide and
4-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]phenyl 1-methylsulphonyl-1-(3-pyridyl)methyl ketone.

8. A process for the preparation of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 which comprises:-

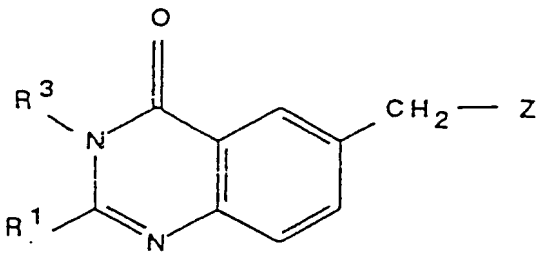
(a) the reaction of an acid of the formula II



II

or a reactive derivative thereof, wherein R^3 is hydrogen or a protecting group, with a compound of the formula Ar^2-CH_2-Q;

(b) the reaction of a compound of the formula III



III

wherein R^3 has the meaning defined above and Z is a displaceable group, with an amine of the formula:

$$HNR^2\text{-}Ar^1\text{-}CO\text{-}CH(Ar^2)(Q)$$

(c) for the production of a compound of the formula I wherein Q is a group which comprises a sulphinyl or sulphonyl group, the oxidation of the corresponding compound of the formula I wherein Q is a group which comprises a thio group;

(d) for the production of a compound of the formula I wherein R^1 is amino-(1-4C)alkyl or substituted-amino-(1-4C)alkyl, the reaction of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl, or a reactive derivative thereof, with ammonia or a substituted-amine;

(e) for the production of a compound of the formula I wherein R^1 is (2-4C)alkanoyloxy-(1-4C)alkyl or substituted-(2-4C)alkanoyloxy-(1-4C)alkyl, the reaction of a compound of the formula I wherein R^1 is hydroxy-(1-4C)alkyl with an acylating reagent; and

(f) for the production of a compound of the formula I wherein Q is a piperazin-1-ylsulphonyl group, the cleavage of a compound of the formula I wherein Q is a 4-(1-4C)alkoxycarbonylpiperazin-1-yl group;

and when a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained by reaction of said compound with a suitable acid or base using a conventional procedure; and when an optically active form of a compound of the formula I is required, it may be obtained by carring out one of the aforesaid processes using an optically active starting material, or by resolution of a racemic form of said compound using a conventional procedure.

9. A pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically-acceptable diluent or carrier.

10. The use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 7 in the manufacture of a novel medicament for use in the production of an anti-tumour effect in a warm-blooded animal.

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